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High Performance Computing in Multiscale Modeling Cardiac Contraction: Bridging Proteins to Cells to Whole Heart

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The availability of increased computing with thousands of computational cores enables new classes of biological models that include detailed representations of proteins and protein complexes with spatial interactions. We develop such a model of the interaction of actin and myosin in the cardiac sarcomere. The model includes explicit representations of actin, myosin, and regulatory proteins. Although this is not an atomic-scale model, as would be the case for molecular dynamics simulations, the model seeks to represent spatial interactions between protein complexes that are thought to produce characteristic cardiac muscle responses at larger scales. While the model simulates the microscopic scale, when model results are extrapolated to larger structures, the model recapitulates complex, nonlinear behavior such as the steep calcium sensitivity of developed force in muscle structures. The model provides a plausible and quantitative explanation for several unexplained phenomena observed at the tissue level in cardiac muscles. Model execution entails Monte-Carlo-based simulations of Markov representations of calcium regulation and actin-myosin interactions. The model is computationally expensive and requires a supercomputer to simulate sub-cellular structures. While useful to understand biophysical questions, such models are obviously impractical to model the billions of cells that comprise a whole human heart. We have also developed a more computationally efficient model that approximated the spatial interactions at the protein level without explicit computation. The goal of this work is to bridge from cells to large organ-level anatomical structures with practical run times. We hope that the power of this approximate model to recapitulate complex force responses in cardiac tissue will foster wider use of cardiac models for research and clinical applications. The work is a case study in multiscale biological modeling where the development of a complex, detailed model is required to guide the development of more abstract and computationally efficient representations.

1 Introduction

Many cardiac phenomenon emerge where effects span extreme spatial and time scales. For example, many cardiac drugs operate on the molecular scale with effects on ionic channels, whereas one wants to understand the effects of these drugs on arrhythmias and sudden cardiac death (i.e., the effects at organism and whole heart level over a much longer time scale). Hence, the cardiac field requires models that can span large spatial and temporal scales¹. The talk presented a body of work around several multiscale models of contraction in heart that attempt to represent the system at different levels of abstraction. The first model is a highly detailed representation of the molecular interactions on a single pair of filaments. This level of detail is required because important controversies exist as to the fundamental molecular mechanisms and how to represent these mathematically². Later, the single filaments are combined into a larger structure called a myofibril. The detailed model also guides the development of abstractions that are computationally efficient and based on ordinary differential equations (ODEs).

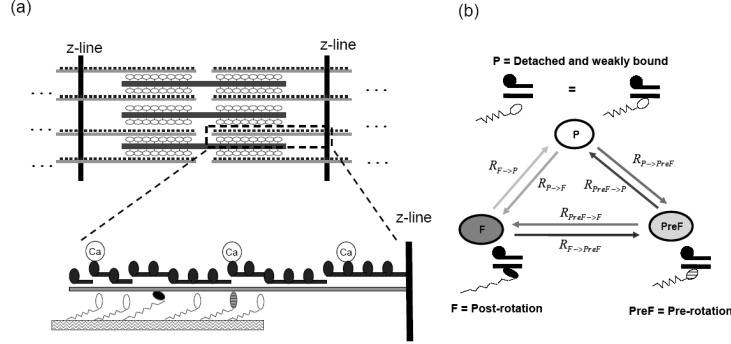


Figure 1. Sarcomere structure in striated muscle. (a) Schematic representation of the repeating sarcomere structure in striated muscle. The sarcomere is defined from z-line to z-line with interdigitated thick and thin filaments that can interact to produce force. (b) State diagram for crossbridge cycling.

2 Mechanistic Model of the Myofilaments

A detailed representation of proteins and protein complexes with spatial interactions is developed to understand fundamental mechanisms in heart contraction⁵. Here the proteins cannot be tractably modeled on first principles based on atomistic approaches such as molecular dynamics. Instead, a more abstract formulation is used. Specifically, the interactions of actin and myosin within one pair of thick and thin filaments in the cardiac sarcomere are represented in Fig. 1a. The sarcomere is the basic repeating of the contractile apparatus in striated muscle. Hence, the model represents a small but repeating structure so that results can be extrapolated to compare with complete muscle responses if one assumes all sarcomeres act equivalently, an assumption that is roughly true for some conditions.

The model includes explicit representations of actin, myosin, and regulatory proteins. For the sake of brevity, we will focus on the actin and myosin interactions. The thin filament is a two-stranded helix of actin (see Fig. 2a). Myosin has three major structural subunits - the head, neck and tail. The head attaches to a binding site and rotates using the energy from the conversion of adenosine tri-phosphate (ATP) to adenosine di-phosphate (ADP) and inorganic phosphate (P_i), a common energy-liberating reaction in cells. The tail regions of myosin assemble together to form the thick filament (see Fig. 2a). The bound linkages between actin and myosin are commonly termed crossbridges to reflect bridging between thick and thin filaments. Figure 1b shows a Markov model for the crossbridge cycle. State **P** is a detached crossbridge which corresponds to two biochemical states: completely separate and a transient, electrostatic interaction known as weakly bound. State **PreF** stands for Pre-Force and corresponds to a more strongly bound state in which the head has not rotated yet. Rotating the head can stretch the extensible neck region to generate force as represented by State **PostF** that stands for Post-Force.

The model contains multiple instances of myosin and the corresponding binding sites as adapted from the work of Daniel and colleagues³. We have used this approach to form the spatial layout of myosin and actin binding sites with the appropriate compliances be-

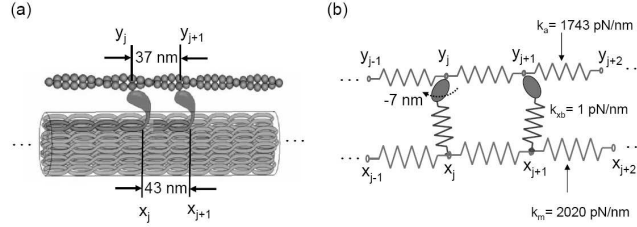


Figure 2. Spatial arrangement of actin-myosin interactions. (a) Myosin heads on the thick filament have an intrinsic spacing of 43 nm, slightly larger than the 37-nm effective spacing of appropriately aligned actin binding sites on the thin filament. (b) Compliances in the thick and thin filaments represented as a system of springs between adjacent binding sites. Attached crossbridges are shown as springs linking the two filaments. Values for actin binding sites (y_i) and myosins (x_i) are computed and modeled as a system of linear springs. Rotation of myosin head changes stretch of crossbridge spring by 7 nm (see text for details).

tween the elements. We assume that the thick filament has myosin heads with appropriate orientations at an intrinsic spacing of 43 nm, as shown in Fig. 2a. In real myosin, the heads extend in a helical fashion such that only a subset will appropriately align to interact with the single thin filament assumed in this model. Note, however, that the 43-nm intrinsic spacing of myosin is slightly larger than the 37-nm spacing of appropriate binding sites on the thin filament. Similarly to the case with myosin, the helical nature of the actin will restrict binding to a subset of actin monomers that appropriately face the thick filament in the two-filament model presented here.

The transition rates between the crossbridge states in Fig. 1b are determined by energy profiles as defined elsewhere⁵. Briefly, the energy profile represent a coupled chemical and mechanical system so that the energy of the hydrolysis of ATP is assumed to permit attachment and rotation of the myosin head. The model correspond to molecular-level events so both forward and reverse rates are assumed. The rates depend on the relative positions of the actin binding sites (y_i) and myosin (x_i) for a given pairing. The attached states (**PreF** and **PostF**) have a parabolic energy profile that corresponds to a spring element. The rates may also depend on metabolite concentration (ATP, ADP, and P_i), although these are not varied in the current version of the model. At each time step in the Monte Carlo simulation, the state of each interacting pair of actin binding site and myosin are updated. The spatial positions of the sites are calculated by solving the linear system of springs for the whole ensemble (Fig. 2b shows a small subset with only two pairs). Note that the rotation of the head (from State **PreF** to **PostF**) is assumed stretch of crossbridge spring by 7 nm. Likewise, reverse rotation (from State **PostF** to **PreF**) decreases the stretch. Different intrinsic spacing of actin binding sites and myosin will produce a distribution of relative positions and transition rates. Moreover, the net motions of the thick and thin filaments that occur during contraction will continually change the relative spacings actin sites and myosin.

The interaction of actin and myosin is controlled by regulatory proteins that binds calcium (Ca) ions. The regulatory proteins (specifically known as troponin and tropomyosin) reside in the two grooves of the two-stranded actin helix and serve to allosterically block interactions between actin and myosin. The term "allosteric" refers to a change in shape and activity of a protein that results from molecular binding with a regulatory substance.

In the lower half Fig. 1a, we represent a single one-dimension lattice of regulatory units that reside on one of the two grooves. The allosteric shift is schematically illustrated by showing some units raised above the thin filament. The important feature of troponin is that it can bind one Ca ion at a single binding site that controls the allosteric switching behavior. The troponin and tropomyosin molecules overlap in an end-to-end fashion and are thought to communicate with their neighbors via this physical communication, a phenomenon called cooperativity. Hence, the regulatory proteins tend to switch on and off in unison with their neighbors. The communication is critical to produce a steep Ca sensitivity in that a small change in Ca level produces a large change in activation level. While space does not permit more description, the details can be found elsewhere^{2,5}.

3 Expanding to Terascale Models

One method of generating multiscale models is to use large computers to solve many replicates of the fundamental structure. Along these lines, the basic model (one thin filament and half of thick filament) just described will be expanded to produce a model of the myofibril (a common experimental preparation that can be dissected from cells). Figure 3 shows a possible mapping of 32 sarcomeres onto one rack of a Blue Gene/L. The simulation of two thick and eight thin filaments is executed on a dual-core processor. Each thick filament is surrounded by six thin filaments, while each thin filament is surrounded by three thick filaments. This gives a filament ratio of two to one, which must be increased to a ratio of four thin filaments to one thick filament in order to account for the left and right sides of a sarcomere. Note that the thick filaments are double-ended and require roughly twice the computation of the half thick filament in the preliminary model. We anticipate a 64-thick and 256-thin filament to represent a full sarcomere at the level of a computer node card. A myofibril model can then comprise 32 full sarcomeres modeled at the level of a full rack of Blue Gene/L. The mapping is approximate because the final implementation may require some redistribution of the model among computation units at the level of processors or node cards.

One challenge to implement large models on large-scale parallel computers is to efficiently use the hardware in a distributed fashion. One method to is to use existing libraries that allow for distributed processing of sparse matrices. We are using PETSc (Portable, Extensible Toolkit for Scientific Computation)⁶. To solve for the locations of the binding sites, the system $\mathbf{A} \bullet \mathbf{X} = \mathbf{k}$ must be solved at each time step where there is a change in state of the crossbridge attachment. PETSc provides a convenient method to construct the sparse matrices and solve the system in a parallel fashion.

4 Approximate Model Based on Ordinary Differential Equations

We have also developed a more computational efficient model that approximated the spatial interactions at the protein level without explicit computation of the spatial interactions⁴. The goal of this work is to bridge from cells to large organ-level anatomical structures with practical run times. Conceptionally, this approximate modeling can be compared to coarse-grain methods in protein folding that are developed be much more efficient than atomistic molecular dynamics approaches. However, one must understand and carefully

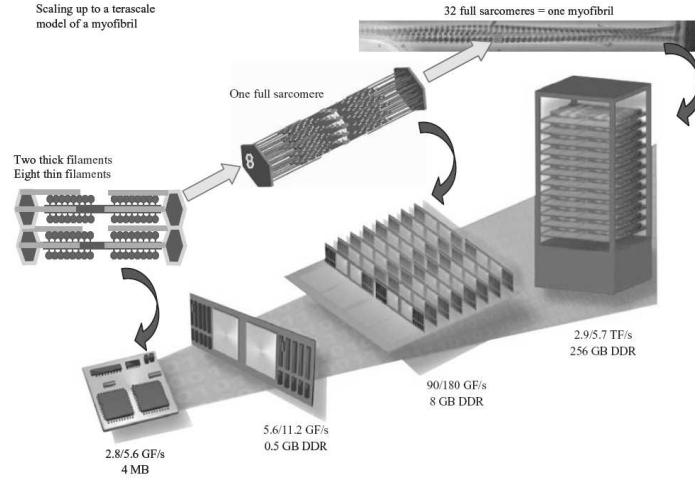


Figure 3. Possible mapping of a 32-sarcomere myofibril model onto one rack of a Blue Gene/L supercomputer. Simulation of two thick and eight thin filaments is executed on a dual-core processor; then, 64 thick and 256 thin filaments can represent a full sarcomere at the level of a node card. The mapping is approximate because a final implementation may require some redistribution of the model among computation units at the level of processors or node cards, in order to balance computational loads, given communication constraints. (DDR: double-data-rate synchronous dynamic random access memory; GB: gigabytes; GF: gigaflops; TF: teraflops.)

weigh the benefits of these approaches as the coarse graining typically trades accuracy and generality for a faster approximate method that works under limited conditions.

The method of transferring a model that is spatially explicit to one that is essentially a non-spatial point model involves representing the mass action of populations rather than individual elements. Such an approach can be done with high accuracy when the individual events are independent. For example, populations of independent membrane-bound channels can be represented in high accuracy as probabilities of state occupancies. In this way, Markov-state diagrams (similar to that in Fig. 1b) can be translated directly into systems of ODEs. However, the case is not so simple for muscle in which many of the important behaviors are thought to emerge from the interaction between neighboring entities². The exact method for translating to a system of ODEs is given elsewhere⁴; however, a brief description is provided here. The ODE-based model represents the populations of crossbridges in the states shown in Fig. 1b. In addition, the mean strains of the attached crossbridge states (**PreF** and **PostF**) are computed using phenomenological formulations. The force is computed at mean occupancies multiplied by the mean strain of the attached states with the assumption of an ideal spring constant. This is an approximation as the real system will have attachment rates and strains corresponding to individual crossbridges. Hence, the calculation of the mean values (a construction often termed "mean field") is an approximation that suffices under restricted conditions.

We hope that the power of this approximate model to recapitulate complex force responses in cardiac tissue will foster wider use of cardiac models for research and clinical applications. Indeed, the talk presented some preliminary results in a coupled electro-mechanical model by Viatcheslav Gurev and Natalia Trayanova at The Johns Hopkins

University. In the whole heart, the ODE-based model provides the mapping between length, shortening velocity, and force during contraction. While preliminary, the results illustrates the work required to developed multiscale models can pay off in improved accuracy at larger scales. In this study, the diffences in timing between contraction at inside (endocardium) and outside (epicardium) of the heart could be recapitulated. Similar results have not been reported previously with phenomenological modeling approaches.

5 Concluding Remarks

The work is a case study in multiscale biological modeling where the development of a complex, detailed model was required to guide the later development of a more abstract and computationally efficient representation. The detailed model seeks to represent spatial interactions between protein complexes that are thought to produce characteristic cardiac muscle responses at larger scales. We have also developed a more computationally efficient model that approximates the spatial interactions at the protein level without explicit computation. The goal of this work is to bridge from cells to large organ-level anatomical structures with practical run times. We hope that the power of this approximate model to recapitulate complex force responses in cardiac tissue will foster wider use of cardiac models for research and clinical applications.

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